REMARKS

In the claims

Applicants have canceled claims 6, 8-11, 16, 22, 26, 29, 30, 52, 53, and 58 without disclaimer or prejudice. Applicants reserve the right to file a continuation application or to take such other action to preserve their rights to the canceled subject matter. Applicants respectfully request that the Examiner enter the preceding amendments.

Rejections under Obviousness-Type Double Patenting

Claims 6, 8-11, 16, 22, 26-29, 35-42, 44-50, and 52-59 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over: claims 1 and 28 of U.S. Patent No. 6,565,831B1 (the '831 patent) in view of Smith, Exp. Opin. Invest. Drugs, 2000, Vol. 9, No. 2, 311-327 (the "Smith reference") or claims 1, 2-8, 13-20, and 24-34 of Lee et al., U.S. Patent No. 6,136,307A (the '307 patent) in view of the Smith reference.

Because Applicants have canceled claims 6, 8-11, 16, 22, 26, 29, 52, 53, and 58, the corresponding rejections are moot. The Examiner is respectfully requested to withdraw the corresponding rejections.

Embodiments of the present invention are recited in independent claims 27 and 28:

27. A method for preventing a ras-activated neoplasm in a subject from developing drug resistance to a chemotherapeutic agent, comprising:

(a) administering, to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent, an effective amount of reovirus under conditions which result in infection of the ras-activated neoplasm by the reovirus; and

(b) administering to the subject an effective amount of the chemotherapeutic agent, wherein the infection prevents the ras-activated neoplasm from developing drug resistance to the chemotherapeutic agent.

28. A method for preventing a ras-activated neoplasm in a subject from developing drug resistance to a chemotherapeutic agent, comprising:

(a) determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent;

(b) administering to the subject an effective amount of reovirus under conditions which result in infection of the ras-activated neoplasm by the reovirus; and

(c) administering to the subject an effective amount of the chemotherapeutic agent, wherein the infection prevents the ras-activated neoplasm from developing drug resistance to the chemotherapeutic agent.

Thus, claim 27 is directed in part to administering, to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent, an effective amount of reovirus. Also, claim 28 recites an independent, active step of determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. As defined in the specification, a neoplastic cell that is refractory to a chemotherapeutic agent is a neoplastic cell not killed or growth inhibited by the chemotherapeutic agent (page 11, line 14).

On the other hand, claim 1 of the '831 patent recites:

1. A method of treating a ras-mediated neoplasm in a mammal, comprising the steps of: a) performing a step selected from the group consisting of: i) administering to the neoplastic cells in said mammal an effective amount of an immune suppressive agent; ii) removing anti-reovirus antibodies from said mammal; iii) administering anti-antireovirus antibodies to said mammal; and iv) suppressing the immune system of the mammal; and b) administering to the neoplastic cells in said mammal an effective amount of one or more reoviruses under conditions which result in substantial lysis of the neoplastic cells.

Also, claim 1 of the'307 patent recites:

1. A method of treating a ras-mediated proliferative disorder in a mammal suffering from said disorder, wherein said mammal is selected from the group consisting of dogs, cats, sheep, goats, cattle, horses, pigs, humans and non-human primates, and wherein said method comprises administering to said mammal an effective amount of at least one reovirus in the absence of BCNU under conditions which result in substantial lysis of the ras-mediated proliferating cells in said mammal.

Neither these claims nor any other claims in the '831 or '307 patents teach or suggest drug resistance, let alone to direct treatment to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent, as claimed in claim 27. Moreover, no

claim in the '831 or '307 patents teaches or suggests cells that are refractory to a chemotherapeutic agent, let alone a step of determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, as claimed in claim 28.

The Smith reference does not remedy these defects. The Smith reference teaches, in part that reovirus infection, in combination with chemotherapy, produced a rate of 80% complete tumor remission (page 319, section 7, 1st paragraph) and teaches that combinations of cisplatin or 5-fluorouracil with ONYX-015, or cisplatin with HSV were superior to either agent alone, and concludes that viral therapy may be added to chemotherapy agents without affecting anticancer efficacy (page 321, section 9, 1st paragraph). However, the Smith reference does not teach or suggest the concepts of drug resistance or of ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, let alone the specific elements of claims 27 or 28.

Consequently, because none of the '831 or '307 patent claims or the Smith reference teach or suggest the concept of drug resistance, they cannot teach the directed method of claim 27. In particular, none of the '831 or '307 patent claims or the Smith reference teach or suggest that treatment should be specifically directed to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent, as claimed in claim 27.

Moreover, because none of the cited references teach or suggest ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, nor do they teach a step of determining if refractory cells are present, they cannot teach or suggest the invention as claimed in claim 28. The Examiner alleges that Applicants argued that "identifying a subject including ras-activated neoplastic cells susceptible to a chemotherapeutic agent or refractory to a chemotherapeutic agent occurs inherently during the treatment of a subject who comprises neoplastic cells susceptible to a chemotherapeutic agent or refractory to a chemotherapeutic agent." (Office Action, page 3, #6). However, this does not constitute the determining step of claim 28. First, none of the '831 or '307 patent claims or the Smith reference teach or suggest refractory cells. Moreover, none of the '831 or '307 patent claims or the Smith reference include the determining step of the invention. As defined in the specification, the determining step includes determining

the growth rate of the cell in the presence or absence of the chemotherapeutic agent, whereby a neoplastic cell is not growth inhibited by the chemotherapeutic agent (and thus the cell is not refractory) if the growth rate is not significantly different with or without the chemotherapeutic agent. (page 11, lines 14-19). In particular, none of none of the '831 or '307 patent claims or the Smith reference teach or suggest the step of determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, as claimed in claim 28.

Consequently, claims 27 and 28 are nonobvious over the claims of the '831 patent and the claims of the '307 patent, either alone or in combination with the Smith reference. Because claims 27 and 28 are independent and nonobvious, their dependent claims are also nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); MPEP 2143.03.

For at least these reasons, the instant claims are nonobvious over the claims of the '831 patent and the claims of the '307 patent, either alone or in combination with the Smith reference. Applicants respectfully request withdrawal of the corresponding rejection under the judicially created doctrine of obviousness-type double patenting.

Rejections under 35 U.S.C. § 102(a)

Claims 27, 35-42, and 52-57 stand rejected under 35 U.S.C. § 102(a) as being anticipated by the '307 patent, or alternatively, as being anticipated by WO00/50051A2 (the '051 application).

As noted above, independent claim 27 is specifically directed to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent. Because neither the '307 patent nor the '051 application teach or suggest the development of drug resistance, they cannot teach the specifically directed method of claim 27. Consequently, claim 27 and its dependent claims 35-42, 54 and 55 are not anticipated by the '307 patent or the '051 application.

Claims 56 and 57 are dependent on claim 28. As noted above, claim 28 includes a step of determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent, an effective amount of reovirus. Because neither the '307 patent nor the '051 application teach or suggest cells that are refractory to a chemotherapeutic agent, they cannot teach the invention claimed in claim 28 or its dependent claims. Moreover, neither the '307 patent nor the '051 application teach or suggest the determining step of the invention. As noted above, the determining step defined in the specification includes determining the growth rate of the cell in the presence or absence of the chemotherapeutic agent, whereby a neoplastic cell is not growth inhibited by the chemotherapeutic agent (the cell is refractory) if the growth rate is not significantly different with or without the chemotherapeutic agent. (page 11, lines 14-19). Because this step is not taught in the '307 patent or the '051 application, neither claim 28 nor its dependent claims 56 or 57 are anticipated.

For at least these reasons, claims 27, 35-42, and 54-57 are not anticipated by the '307 patent or the '051 application. Moreover, the rejections are moot with respect to claims 52 and 53, which Applicants have canceled. The Examiner is respectfully requested to withdraw the corresponding rejections.

Rejections under 35 U.S.C. § 103(a)

Claims 6, 8-11, 16, 22, 26-29, 35-42, 44-50, and 52-59 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over the '307 patent or the '051 application or over Mercer University Home page 1996, pp 1-2 (the "Mercer reference," www.mercer.edu/publications/discoveries/96-97/cancer.htm accessed June 18, 2004) in view of the Smith reference.

The rejections are moot with respect to claims 6, 8-11, 16, 22, 26, 29, 52, 53, and 58, which Applicants have canceled. The Examiner is respectfully requested to withdraw the corresponding rejections.

Further, as noted above, neither the '307 patent nor the '051 application teach or suggest drug resistance or cells that are refractory to a chemotherapeutic agent. Moreover, the Mercer reference does not teach or suggest drug resistance or cells that are refractory to a chemotherapeutic agent. Consequently, none of these references teach or suggest the directed treatment of claim 27, which includes administering, to a subject having a ras-activated neoplasm capable of developing drug resistance to a chemotherapeutic agent, an effective amount of reovirus. Also, none of these references teach or suggest claim 28's step of determining, in a subject having a ras-activated neoplasm, if the ras activated neoplasm includes ras-activated neoplastic cells that are refractory to a chemotherapeutic agent. Finally, as noted above, the Smith reference cannot remedy these defects.

For at least these reasons, the claims are unobvious over the '307 patent or the '051 application or over the Mercer reference in view of the Smith reference. The Examiner is respectfully requested to withdraw the corresponding rejections.

Rejections under 35 U.S.C. § 112

Claims 30, 43, and 51 stand rejected under 35 U.S.C. § 112. The Examiner alleges that these claims, directed to a method for preventing a ras-mediated neoplasm from developing drug resistance to a second chemotherapeutic agent, are not enabled.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. MPEP §2164.01; *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). Factors to be considered (MPEP 2164.01(a)) to support a determination that a disclosure is enabling and that undue experimentation is not required include, for example:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Evaluation of "undue experimentation" is not a single, simple factual determination, but is reached by weighing the above factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. MPEP 2164.01(a).

Breadth or scope of the claims; nature of the invention

The claimed invention includes methods for preventing a ras-activated neoplasm in a subject from developing drug resistance to a chemotherapeutic agent. In the rejected claims, the invention is also directed to preventing the ras-activated neoplasm from developing drug resistance to a second chemotherapeutic agent.

State of the prior art

The state of the prior art is that it is known that some cancerous tumors can become resistant to one or more chemotherapeutic agents, even structurally unrelated agents. One of ordinary skill in the art routinely administers a second chemotherapeutic agent to a tumor that becomes resistant to a first chemotherapeutic agent.

Level of ordinary skill in the art

The level of ordinary skill in the art is high, and one of ordinary skill in the art routinely conducts a significant amount of experimentation.

Predictability, working examples and amount of guidance in the specification

The Examiner alleges that the specification does not teach that the methods can prevent the neoplasm from developing drug resistance to another unknown chemotherapeutic agent. The Examiner alleges that the specification does not give guidance as to how to predict or measure whether the reovirus treatment can be used for preventing drug resistance to an unknown second chemotherapeutic agent.

The specification teaches in a working example (Example 1) that reovirus can be used for increasing the sensitivity of ras-activated neoplastic cells to a representative chemotherapeutic agent, cisplatin. The guidance of the specification, e.g., in Example 1, is enabling for determining the efficacy of chemotherapeutic agents generally. Moreover, the specification teaches that:

> Preferably, administration of the reovirus prevents the neoplasm from developing drug resistance to multiple drugs, including structurally unrelated drugs. Accordingly, a preferred embodiment of the present invention provides a method for preventing a neoplasm in a subject from developing drug resistance to a chemotherapeutic agent wherein drug resistance to a second chemotherapeutic agent is also prevented (page 9, lines 7-12)

Because it is routine in the art to supplement the use of a first therapeutic agent such as cisplatin with a second chemotherapeutic agent, it would be a simple matter for one of ordinary skill in the art to adapt the teaching of the specification with respect to a first chemotherapeutic agent to measure the efficacy in preventing resistance to a second chemotherapeutic agent.

Moreover, it is not necessary to predict whether the reovirus treatment can be used for preventing drug resistance to an unknown second chemotherapeutic agent. As one of ordinary skill in the art knows, a tumor can become resistant to one or more chemotherapeutic agents, even structurally unrelated agents. However, as taught in the specification, the method is believed to operate by a general mechanism:

> Without being limited to a theory, we believe that reovirus sensitizes tumor cells to chemotherapeutic agents by enhancing accumulation of the agents in tumor cells, or by inducing apoptosis. Reovirus is known to inhibit protein synthesis of the host cell in favor of translation of its own proteins. Therefore, reovirus infection may inhibit the synthesis of drug transporter proteins such as MDR1 or the MRPs, and enable drugs to accumulate in the cell. Since drug transporter proteins are responsible for transporting various drugs out of the cell, including structurally unrelated drugs, inhibiting the synthesis of such transporter proteins would lead to sensitization of the cell to a variety of drugs. (page 19, line 11)

Consequently, because the method is believed to operate by a general mechanism, the method can work with a variety of chemotherapeutic agents, even structurally unrelated ones.

Quantity of experimentation needed to make or use the invention based on the disclosure

As noted above, the level of skill in the art is high, and a person of ordinary skill in the art routinely conducts significant amounts of experimentation. In particular, because of the development of drug resistance, one of ordinary skill in the art can routinely employ more than one chemotherapeutic agent in treating a single tumor or a single subject. One of ordinary skill in the art can readily adapt the working example in the specification to the use of a second chemotherapeutic agent. The same techniques that can be used to administer and measure the efficacy of a first chemotherapeutic agent can be used to administer and measure the efficacy of a second chemotherapeutic agent. Consequently, the amount of experimentation needed to adapt the teaching of the specification to prevent the development of resistance to a second chemotherapeutic agent is not significantly greater than the amount of experimentation ordinarily performed in the art. Therefore, one of ordinary skill in the art could make or use the claimed invention given the disclosure in the application, coupled with information known in the art, without undue experimentation.

For at least these reasons, the specification is enabling for preventing the development of resistance to a second chemotherapeutic agent as claimed in claims 43 and 51. The rejection is moot with respect to claim 30, which Applicants have canceled. Applicants respectfully request that the corresponding rejections be withdrawn.

Conclusion

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims of this application at an early date is earnestly solicited.

No fee is believed to be due. If, however, there are any charges or credits, please apply them to Deposit Account No. 06-1050.

Respectfully submitted,

Date: January 17, 2007

Kraig Anderson
Reg. No. 54,916

Customer No. 26181
Fish & Richardson P.C.
Telephone: (650) 839-5070
Facsimile: (650) 839-5071

50390241.doc